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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,393	07/10/2001	Keith D. Allen	R-387	9468

26619 7590 01/24/2005

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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,393	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-48* is/are rejected.

7)☒ Claim(s) *45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Examiner of Record has changed and is now Thaian N. Ton of Art Unit 1632.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/9/04 has been entered.

Applicants' Amendment, filed 12/9/04, has been entered. Claims 36-48 have been added, are currently pending and under examination.

Specification

The prior objection to the specification with regard to the improper incorporation of subject matter is maintained for reasons of record. Applicants argue that MPEP §608.01(p) provides the guidelines for the proper incorporation by reference and that pending U.S. Applications may be used for incorporation by reference. Further, Applicants argue that 1) the disclosure provides sufficient enabling description of the essential material Applicants are attempting to incorporate and 2) that the incorporation by reference of commonly assigned U.S> patent applications is proper. See pp. 1-2 of Applicants' Response.

This is partially persuasive. The Examiner agrees that the incorporation by reference of pending U.S. Applications is provided for by the MPEP, however, there is no evidence of record that these U.S. Applications cited in the specification are commonly assigned and the Examiner is unable to ascertain that these references are indeed commonly assigned, as asserted by Applicants. Finally, it is noted that the specification refers to Application No. 08/971,310. Upon review, it is found that this case was converted to provisional 60/084,194. Applicants should amend the specification to reflect this change, as well as the fact that both of the provisional applications referred to in the specification are now expired.

Claim Objections

Claim 45 is objected to because of the following informalities: the claim does not end in a period. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Definitions:
[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, or course, be tempered by consideration of the context and nature of the invention. For example, it a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

"Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP § 2107 - 2107.02.

Claims 36-48 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. This rejection is maintained for reasons of record advanced in the prior Office action.

The claims are directed to a transgenic mouse whose genome comprises a null protease-like allele, said allele comprising a coding sequence comprising the sequence of SEQ ID NO: 1; said null allele comprising exogenous DNA, said exogenous DNA comprising a gene encoding a visible marker, wherein said visible marker is capable of expression in the brain. In further embodiments, the claimed invention is directed to methods of making the transgenic mouse and methods of using the transgenic mouse to identify an agent capable of modulating activity of a gene comprising a coding sequence comprising the sequence of SEQ ID NO: 1.

Applicants traverse this rejection because they argue that where an invention has a well-established utility or is useful for any particular practical purpose, the invention fulfills this standard. Applicants argue that the present invention has a well-established utility since a person of ordinary skill in the art would immediately appreciate why knockout mice are useful. Applicants argue that in general, a knockout mouse has the inherent and well-established utility of defining the function and role of a disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations, or properties of the knockout mouse. Applicants argue that the NIH has stated that the knockout mouse is the premier model for determining gene function, and assert that this is a utility that is

specific, substantial, and credible. Finally, Applicants argue that knockout mice are so well-accepted as tools for determining gene function, that various individuals have proposed creating knockout mice for all genes. See pp. 2-5 of Applicants' Response. Applicants argue that which respect to the claims drawn to transgenic mice having a null allele, Applicants provide Austin *et al.*, who state that null-reporter alleles should be created, that they are an, "indispensable starting point for studying the function of every gene." Further, Applicants argue that research tools, such as the instantly claimed knockout mice, are patentable because they have a clear, specific and unquestionable utility, which is to analyze gene function. Applicants further argue that various authors provide support for the asserted utility of the claimed mice, for example, Alberts *et al.* provide teachings to show that knockout mice are "invaluable tools for investigating gene function," Genes VII states that knocking out of a gene is, "[A] powerful method to investigate directly the importance and function of the gene." See pp. 5-7 of the Response. Applicants further argue that the commercial use of the knockout mice has been clearly established because a large pharmaceutical company has ordered the claimed transgenic mice, and that it cannot be reasonably argued that the claimed invention has no "real world use". Applicants submit that one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, and that this utility is found to be specific, substantial, and credible. See p. 7 of the Response.

This is not persuasive. In the instant case, the claimed knockout mice lack utility for the reasons set forth in the previous Office actions. For example, knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. However, the contemplated utilities of using the instant mice to obtain a clue to a pathway is not a considered "substantial utility." Note that it was scientifically well-known to knock out a gene to determine its function or what will happen when the gene is not expressed. This is supported further by Applicants' response. However, scientific "utility" is not the same as "patentable utility" or a "well-established" utility. The MPEP and utility guidelines clearly set forth that a "well-established utility" must be specific, substantial and credible. At the time of filing, knockout mice were used for further research in the art. However, further research does not rise to the level of a "well-established utility" because such a utility is not substantial, specific or credible. With respect to MPEP §2107.01, I (see p. 6 of Applicants' Response), a gas chromatograph is a research tool with a well-defined function and highly specific use that does not necessitate further study of itself. It may be that a gas chromatograph may be used for a wide variety of analyses; however, this does not change its specific use for analyzing a sample. In contrast, the claimed invention is not a general tool for analyzing other samples and, at most, serves to study the function of a single gene. In this respect, the utility of a

knockout mouse cannot be compared to a gas chromatograph. Therefore, the utility of the instant invention is neither specific nor substantial.

The utility guidelines specifically state that further research is not a "substantial utility":

> [T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study of mice would have been required to determine how to use the mouse of Applicants' invention as a model of disease, particularly, because the instant specification fails to disclose any specific disease or condition that is associated with the disruption of a protease-like allele. The mere recitation that the gene is protease-like, does not provide a specific or substantial use for the claimed mice. Furthermore, the lack of specific teaching in the specification with regard to a protease-like allele provides evidence that further study and experimentation would be required in order to determine the association of a disruption of protease-like allele with a specific condition. Note that it is clear from all of the art provided by Applicants that knockout mice are used to elucidate gene function, which is not considered a substantial utility.

The asserted utility is not considered to be specific and substantial because the evidence of record has not provided a correlation between a disruption of the a protease-like allele and the claimed phenotypes of increased sensitivity to pain, increased susceptibility to seizure; thus, the utility of identifying agents that affect said phenotypes (which is an asserted utility of the mice) is not apparent. The evidence and teachings of record fail to provide a nexus between the protease-like allele and any particular disease or disorder associated with it. Furthermore, neither the specification nor any evidence or teachings of record have provided any other utilities for the claimed transgenic mice that are specific and substantial. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the transgenic mouse encompassed by the claims. Thus, using the mice claimed for further research is not a "substantial utility".

Applicants argue that the disclosed phenotype of the claimed mice, including increased sensitivity to pain and increased susceptibility to seizure provide utility to the claimed mice. Applicants assert that the instant case is similar to arguments made in *In re Brana*. Applicants argue that the claimed invention is useful for a practical purpose, and that this assertion would be considered credible by a person of ordinary skill in the art; because the claimed mice have demonstrated specific phenotypes (increased pain sensitivity and increased seizure susceptibility) and the use of these mice would be considered to be an unbelievable undertaking or to

involve implausible scientific principles. Applicants cite art to show that knockout phenotypes provide accurate information concerning gene function (Doetschman). See pp. 8-9 of the Response.

In response, the fact pattern in *Brana* does not correlate to the fact pattern of the instant application. In *Brana*, the court addressed two separate issues, utility and enablement. The court held that the specification did, in fact, disclose a specific and substantial use for the compound, treating leukemia, and that this use was overlooked by the PTO in making the rejection under 101. The court observed that the claimed compound was similar in structure to compounds in the prior art that were useful in treating leukemia. The claimed compound behaved in a manner similar to that of the prior art in art accepted assays for anti-leukemic activity. Therefore, the specification enabled the use. The instant specification and the art of record fail to support such a patentable utility for the instant invention and therefore, the principles set forth in *In re Brana* do not apply to the instant invention. Furthermore, it is reiterated that the instant invention does not have utility because the mice exhibit a phenotype that fails to be correlated to the function of the limulus clotting factor C, which is a factor in the blood clotting pathway. There is no correlation between the observed phenotypes and the knockout of the limulus clotting factor C gene; thus the utility of these mice are not readily apparent.

Applicants argue that in addition for studying gene function, the claimed transgenic mice are useful for studying gene expression. The claims as amended now recite that the transgenic mice contain a visible marker, such as lacZ. Applicants cite Austin *et al.* to support that studying gene expression using a reporter gene is clearly recognized by those skilled in the art. Further, Applicants remind the Examiner that the claimed invention need only satisfy one of its stated objectives to satisfy the utility and enablement requirements. See pp. 10-11 the Response.

This is not persuasive. In particular, utilizing a visible marker, such as lacZ is a general utility that applies to any knockout mouse and is not specific. It is a widely used technique to generate mouse knockouts by inserting a visible reporter gene into an endogenous gene. Just as any gene can be cloned to study gene expression, any gene can be knocked out using a lacZ construct to study function and/or expression.

In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse and cells encompassed by the claims to be credible, specific or substantial.

Claims 36-48 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and

substantial asserted utility or a well-established for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-48 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record advanced in the prior Office actions.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by

weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Applicants argue that the Examiner has not provided any support for the assertion that the mice produced by the methods disclosed in the specification would not lead to a consistent phenotype. Applicants point to Lariviere (cited in the prior Office action) who state that knockout mice "display significant and sometimes extreme phenotypic differences in many assays of nociception, hypersensitivity and analgesia." Applicants argue that this reference has been improperly applied to the claimed invention Particularly, Applicants argue that Lariviere suggest that the effect of the mice with a 129 ES cell strain and C57BL/6 breeding strain would lead to a 129-like phenotype, that is, a decreased response to pain. The opposite was

observed for the instantly claimed mice, and thus, Applicants argue that it is unlikely that the pain related phenotype observed in the claimed mice would be a result of genetic background differences between the knockout and wild-type mice. Applicants argue that the Examiner has not set forth any reason or rationale to doubt the objective truth of the statements made in the specification, that the influence of genetic background was already factors into their analyses, as to comparison with age-, gender- and strain-matched controls. See p. 12 of the Response.

This is not found to be persuasive. Firstly, Applicants have not pointed to page and line number, wherein it can be found that Lariviere suggest that the claimed mice would lead to a "129-like" phenotype. What Lariviere states is that 129-like knockout mice are seen more often than C57BL/6-like mice; that is, that more mice that appeared to respond like 129-like mice were seen when transgenic mice were tested for nociceptive sensitivity. See pp. 470-471, bridging ¶. It is maintained that the art of record recognizes that different inbred mouse strains react significantly differently to the hotplate test, and that the resulting phenotype of these knockout mice is neither considered routine nor predictable. Furthermore, the specification does not teach that the control with which the claimed mice were compared to were strain matched. See p. 53, lines 1-5, which recites that the mice were compared to age and gender matched wild-type control mice.

Applicants point to the fact that they have now removed the phenotypes from independent claim 36, and that they do not believe that there is a requirement that a claim to a novel composition of matter recite properties (or in this case, phenotypes) of the compositions. Moreover, Applicants argue that predicting phenotypes must be distinguished from the reproducibility of the phenotype of the claimed mouse, and the general rule is that the disruption of the coding sequence by a positive selection marker, will result in a null allele, which involves ablation of gene function, and that ablation of function is expected to result in the same phenotypic response. See pp. 12-13 of the Response.

This is not persuasive. It is maintained (as in prior Office actions) that the state of the art of producing transgenic animals is such that it would not be predictable as to the resulting phenotype of any particular gene disruption. The lack of recitation of particular phenotypes fails to provide an enabled use for the claimed transgenic mice, because one of skill in the art would not know how to use these mice. Note that the art cited by Applicants (Bilkie-Gorzo) support that the resulting phenotype of any particular genetic disruption is also dependent upon genetic background because they teach that Penk1 (-/-) mice on a C57BL/6 background showed elevated levels of anxiety in the light-dark and startle response tests, whereas DBA/2J-Penk1 (-/-) mice showed elevated levels of anxiety in the zero-maze and social interaction tests. Thus, it is clear from this cited art, that different behavioral effects are observed on different backgrounds.

It is noted that the newly added claims now require that the gene disruption create a null allele. The instant specification teaches only one gene disruption and does not show any evidence or characterization of the disruption or the gene product to demonstrate that the disruption disclosed is or even would likely generate a null allele. Gene disruptions can lead to hypomorphic and hypermorphic alleles. The specification does not teach how to make a null protease-like. Without knowing that the allele taught by the specification is a null, due the unpredictability of phenotype inherent in the art of making knockout mice, it cannot be predicted that the mice claimed, having a null allele, will exhibit the same phenotype as the mice taught in the specification. Furthermore, it is noted that the claims fail to be enabled because they recite phenotypes which are only found in specific mice. For example, claim 39 recites that the mice have increased sensitivity to pain and increased sensitivity to seizure. However, the specification teaches that only homozygous mice had these observed phenotypes. Furthermore, the specification fails to provide any phenotype for the claimed heterozygous mice. See claim 37, for example. Without an appropriate phenotype, one of skill in the art would not know how to use these claimed heterozygous mice.

Accordingly, in view of the breadth of the claims and lack of guidance provided by the specification, as well as the unpredictability of the art, one of ordinary skill at the time of the claimed invention it would have required undue

experimentation for one of ordinary skill in the art to make use the claimed invention.

Claims 36-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The claims, as newly amended, recite that the transgenic mouse of the claimed invention comprises a null protease-like allele, wherein the allele comprises a coding sequence comprising the sequence of SEQ ID NO: 1, said null allele comprising exogenous DNA, said exogenous DNA comprising a gene encoding a visible marker, wherein said visible marker is capable of expression in the brain. The claimed transgenic mice (and methods of producing and using the mice) are not described in the instant disclosure. In particular, the instant disclosure is directed to the generation of a particular transgenic mouse, one that comprises a homozygous disruption in the limulus clotting factor protease-like gene using a targeting construct comprising SEQ ID NO: 1. The instant specification fails to describe the breadth of the newly amended claims "a null protease-like allele" in such a way as to enable one skilled in the art to which it pertains, or with which it

is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described. The instant specification fails to describe any other species within the genus of "protease-like allele" as encompassed by the claims, with particularity to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described by the specification and which are not conventional in the art as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that one of skill in the art would recognize that the inventor had possession of the claimed invention. In the instant case, the claimed embodiments of a null protease-like allele lacks a written description because the specification fails to describe what other null protease alleles would fall in this genus, and, when used as claimed, would result in the a particular transgenic mouse with the claimed phenotypes. The skilled artisan could not envision the detailed chemical structure of all such protease-like allele, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. See *Fiers v. Revel,*

25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Furthermore, the claims, as currently amended, fail to provide description for the claimed invention, because they recite a transgenic mouse whose genome comprises a null protease-like allele, wherein the allele comprises a coding sequence comprising the sequence of SEQ ID NO: 1, and the null allele comprises exogenous DNA comprising a gene encoding a visible marker. Applicants point to the specification for support of these amendments. See p. 1 of Applicants' Response for specific page and line numbers. After review of the specification, it is ascertained that specification fails to provide specific support for the amendments, in particular for exogenous DNA comprising a gene encoding a visible marker, and in particular embodiments, where the visible marker is lacZ. See Claims 36 and 42, for example. Expression analysis of LacZ expression (see p. 53 of the specification) describe <u>one species</u> of the claimed mouse, using <u>one</u> specific targeting construct (see Figures 2A-2B) used to make this mouse. This construct comprises both a positive selection marker and a lacZ gene. The expression analysis shows the expression of lacZ in a variety of tissues. However, the instant specification fails to describe a genus of knockout mice, wherein the null protease allele contains a visible marker, as broadly claimed. In fact, the specification only shows that the lacZ gene was the only screenable marker contemplated. Furthermore, it is noted that lacZ is <u>not</u> a visible marker, *per se*. LacZ is a gene that encodes a product, beta-galactosidase,

the presence of which can only be visualized indirectly through an assay that results in the enzymatically produced colored visible product. It is the product of the reaction that is visible, not the lacz or the β-galactosidase. With respect to the visible marker, the specification does not mention, even in passing, a general feature of the claimed invention where the exogenous DNA encodes a visible marker, consequently, recitation of the limitation of "visible marker" in the current context is new matter. See, for example, *In re Shokal*, 113 USPQ 283 (CCPA 1957); Purdue Pharma L.P. v. Faulding Inc, 56 USPQZII 1t81 (CAFC 2000).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

MPEP § 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to

include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" (emphasis added).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 is unclear. The claim recites that the mouse has a genome that comprises a "null protease-like allele". The metes and bounds of this term are not clear. It is unclear how an allele can be "protease-like", because an allele is an alternative form of a gene; thus, it is unclear how a gene can be "protease-like". For example, the resulting peptide could be "protease like". Furthermore, the claim is unclear because it results that the null allele comprises a coding sequence

comprising the sequence of SEQ ID NO:1, and it comprises exogenous DNA wherein the exogenous DNA comprises a gene encoding a visible marker. This is unclear because an allele is part of the mouse's genome, therefore it is unclear how it can comprise exogenous DNA. For example, the allele could have a disruption, wherein the disruption comprises exogenous DNA, but the allele, in and of itself, consists of endogenous DNA. The metes and bounds of the claim are further unclear because if the allele is null, it would not have a coding sequence because the allele is no longer present. Claims 37-48 depend from claim 36.

Claims 36 and 46 recite the phrase "capable of" (see the last line of claim 36, and part (d) of claim 46). This term implies a latent property and the conditions for the latent property must be clearly defined. Therefore, it is unclear if the latent property is ever obtained. The metes and bounds of this term are not defined by the claimed. It is suggested that if this term is meant to imply that a particular action occurs, that the claim be written in active language. Claims 37-48 depend from claim 36; claims 47 and 48 depend from claim 46.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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